



بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ

السَّلَامُ عَلَیْكُمْ وَرَحْمَةُ اللّٰهِ وَبَرَكَاتُهُ

Pain Modulation

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Objectives



- ➔ Describe the control of pain perception including:
 - Spinal modulation (Gate theory of pain control).
 - Supra spinal modulation (Special pain control analgesic system).
 - Pain modulation by opioid neurotransmitters.
- ➔ Sites & mechanism of pain relief

Pain Modulation

- ❖ Pain modulation means pain perception variability (the degree to which a person reacts to pain)
- ❖ Pain modulation is influenced by:
 - Endogenous mechanism
 - Exogenous mechanism

Pain modulation can be discussed under following headings

- ❖ Spinal modulation of pain input:
 - Gate theory of pain
- ❖ Supra spinal modulation (Special pain control analgesic system):
 - Role of periaqueductal grey (PAG) matter
 - Role of Nucleus Raphe Magnus (NRM)
- ❖ Pain modulation by opioid neurotransmitters as: endorphin, enkaphalin, dynorphin.

The gate theory of pain control

Special neurons in the the dorsal horn of spinal cord (SGR) form the gate through which pain impulses must pass to reach brain.

Three variables control this gate:

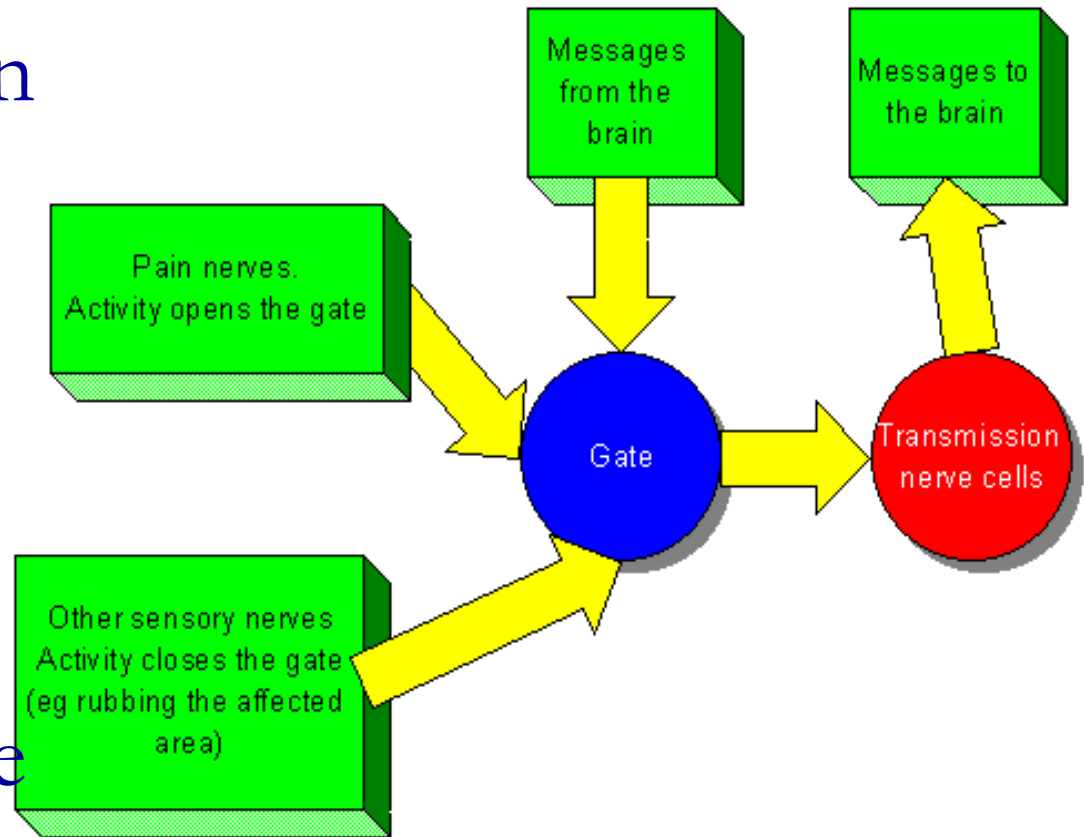
- ✓ A-Delta fibres (fast pain).
- ✓ C- fibres (slow pain).
- ✓ A-Beta fibres (light touch).

Pain Gate Theory

This gate has the ability to block the signals from the A-delta and C fibres preventing them from reaching the brain.

Gate opened or closed by 3 factors:

1. Activity in the pain fibres - opens the gate.
2. Activity in other sensory nerves - closes the gate.
3. Messages from the brain.



The gate theory of pain control (Cont.)

- Impulses coming along type C pain fibers cause the release of substance P from these fibers and tend to open the gate.
- While impulses coming along A β fibers tend to keep the gate closed by process of presynaptic inhibition of C fibers and postsynaptic inhibition of secondary neurons in dorsal horn.

The gate theory of pain control (Cont.)

- If impulses in the C and A-delta fibres are stronger than the A-beta fibres the gate opens.
- If impulses in the A-beta fibres are stronger than the C and A-delta fibres the gate closes.
- A-delta fibres are always stronger.

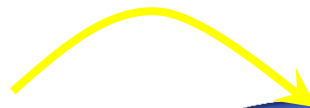
Central Nervous System

A β fibers



Substantia Gelatinosa

Close



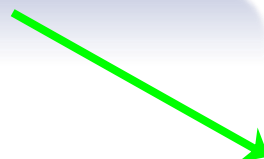
Pain Transmission

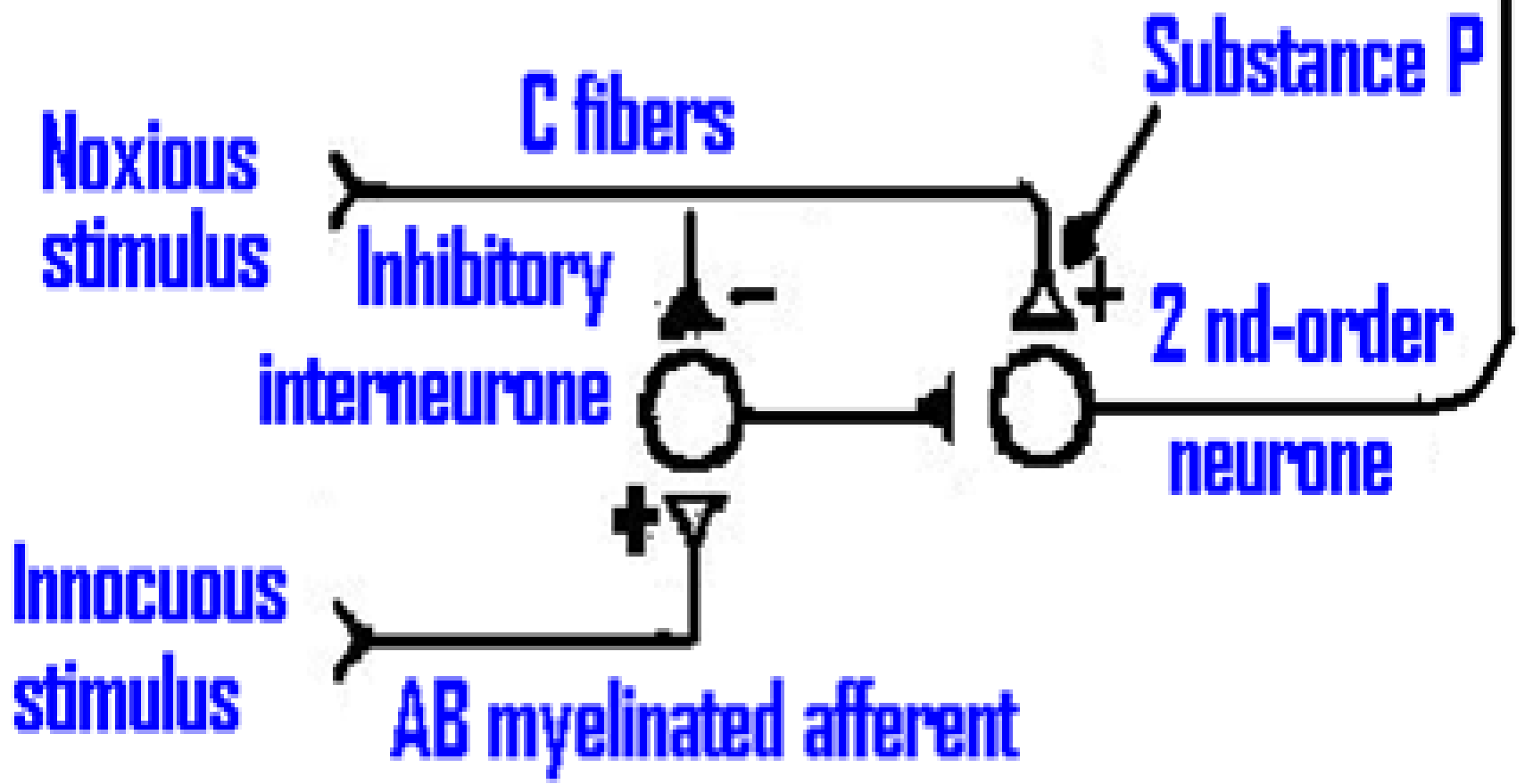
Open



Response

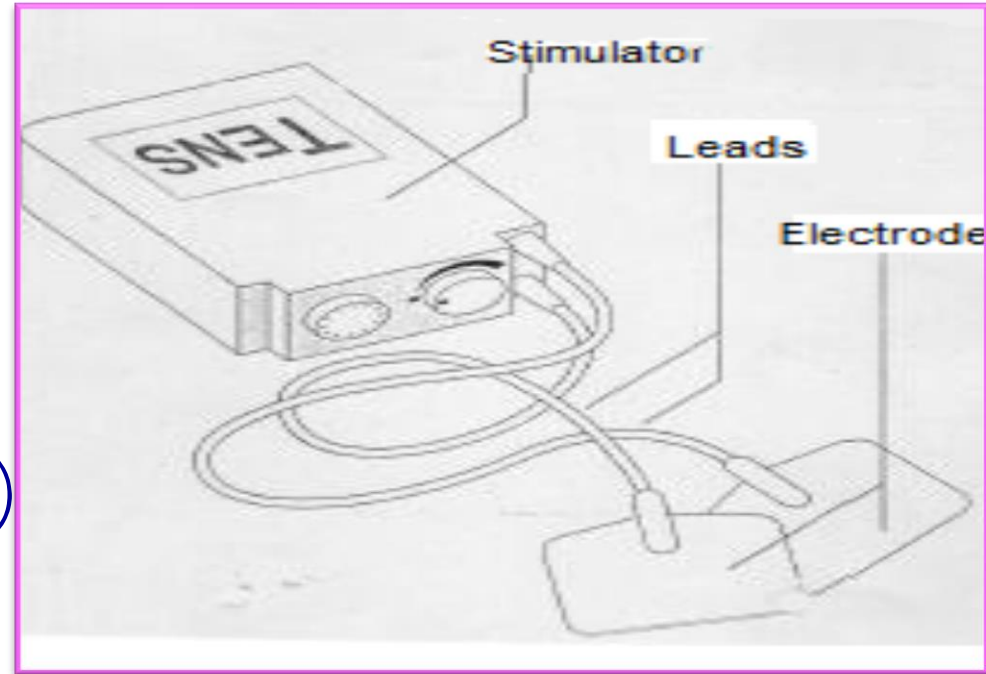
A-delta fibers
C fibers





Gating of pain

- The gate theory explains the pain relief by skin rubbing, shaking the painful part, acupuncture & Trans Cutaneous Electrical Nerve Stimulation (TENS)



- All are supposed to stimulate mechanoreceptors that activate neurons of dorsal column, the collaterals relieve pain.

The gate theory of pain control (Cont.)

- The gate is under control of higher centers.
- Specialised nerve impulses arise in the brain itself and travel down the spinal cord to influence the gate.
- This is called the central control trigger and it can send both inhibitory and excitatory messages to the gate sensitising it to either C or A- β fibres.

The gate theory of pain control (Cont.)

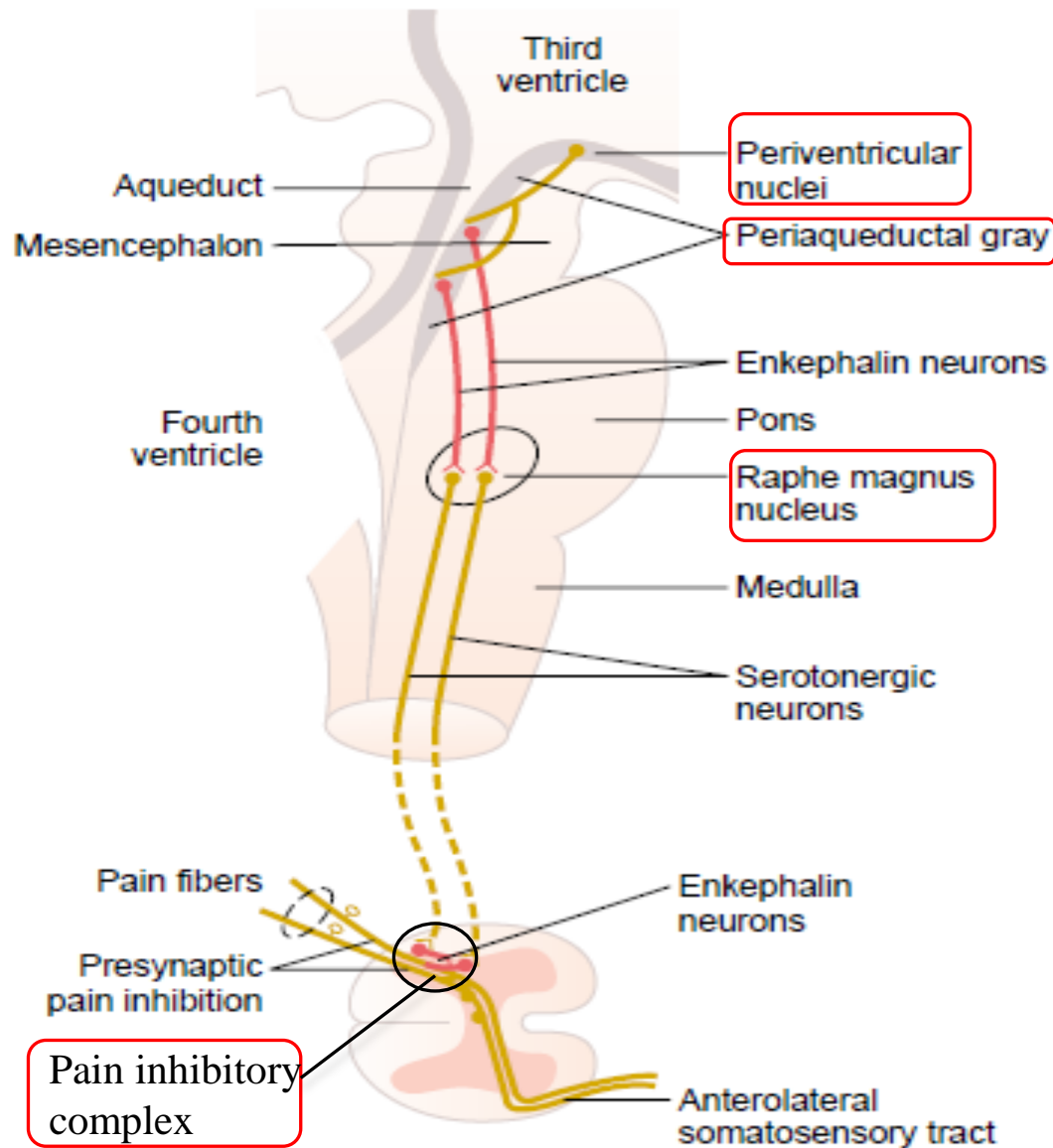
- The inhibitory neurons make a pain blocking agent called enkephalin.
- Enkephalin is an opiate substance similar to heroin which can block Substance P, the neurotransmitter from the C fibres and this keeps the gate closed.

Supra spinal modulation (Special pain control analgesic system)

This is a specific system that blocks pain transmission in CNS. Its major constituents are:

1- The periaqueductal gray and periventricular areas of the mesencephalon and upper pons surround the aqueduct of Sylvius and portions of the third and fourth ventricles.

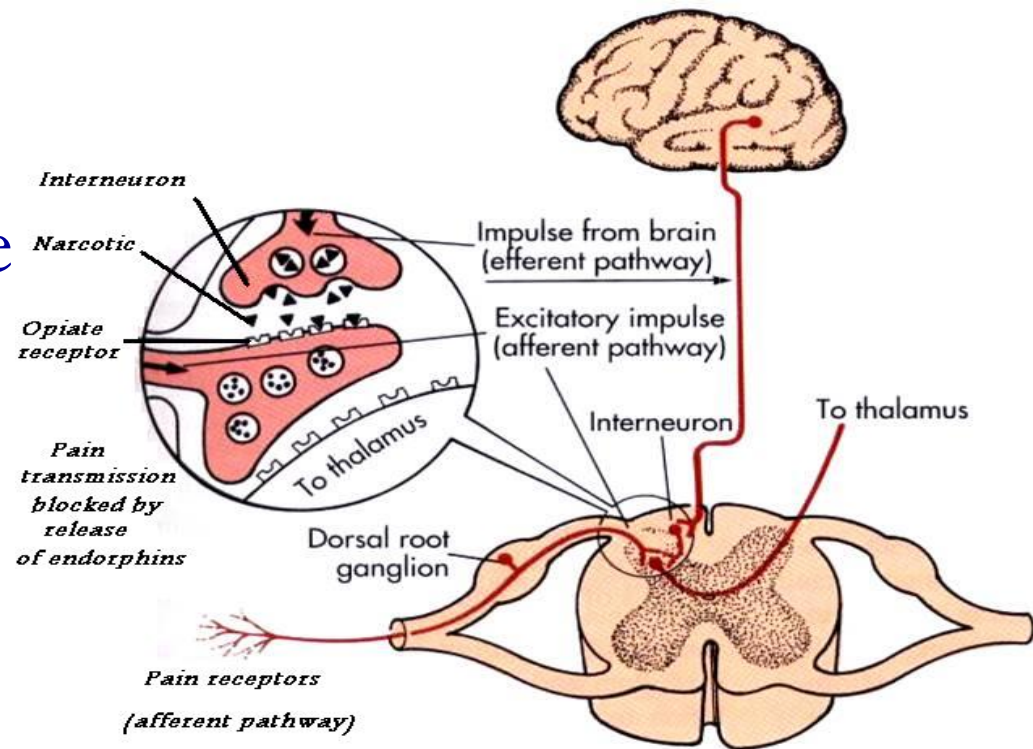
2- Raph magnum nucleus, a thin midline nucleus located in the lower pons and upper medulla, and the nucleus reticularis paragigantocellularis, located laterally in the medulla.



Analgesia system of the brain and spinal cord, showing (1) inhibition of incoming pain signals at the cord level and (2) presence of *enkephalin-secreting neurons* that suppress pain signals in both the cord and the brain stem.

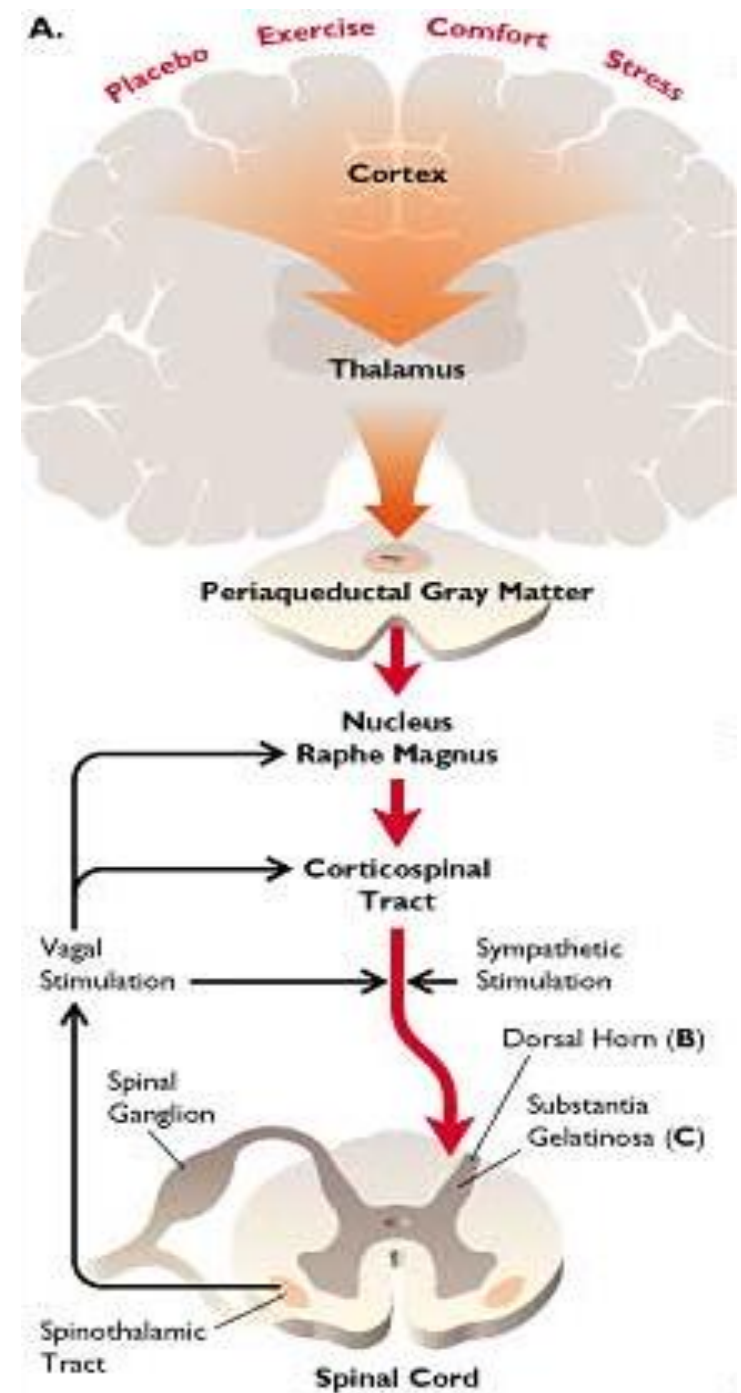
3- Pain inhibitory complex in dorsal horn of SC.

- It consists of multiple short encephalinergetic neurons that terminate on central endings of pain conducting afferent fibers.
- When stimulated, enkephalin release.
- Enkephalin cause pre & postsynaptic inhibition of pain transmission.



Analgesia occurs as follows:

- Periaqueductal grey area receives neuronal inputs from thalamus, hypothalamus, cerebral cortex.
- PAG projects neurons containing aspartate & glutamate that stimulate raph magnus nucleus (RMN)
- RMN projects serotonergic neurons, this in addition to noradrenergic neurons project from adjacent medulla to dorsal horn. They block pain signals by activating PIC.



Opioid receptor modulation

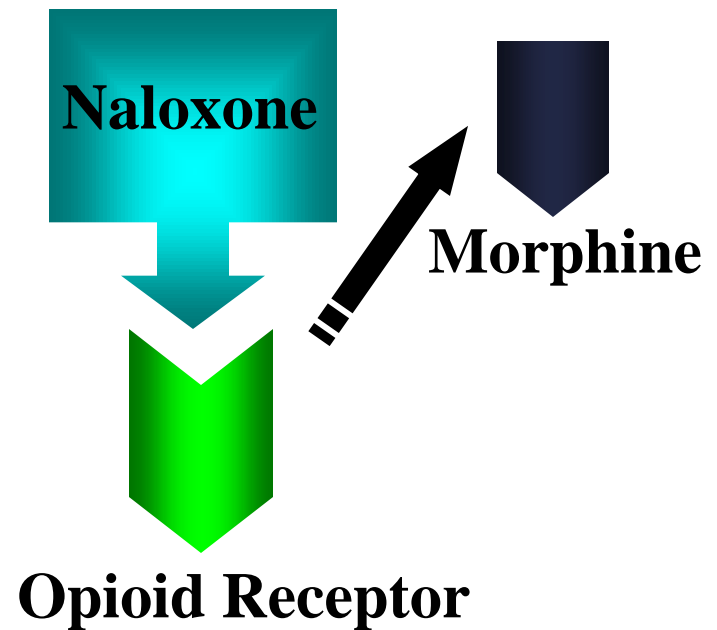
- Opioid peptides are morphine-like substances present in body.
- They are natural analgesic substances that act by binding to opiate receptors in analgesic system and dorsal horn of SC on central ending of pain conducting pain fibers.

Mechanism of opioid neurotransmitter action:

- **Endorphin:** Neurons using endorphin or enkaphalin are found in PAG where they inhibit GABAergic interneurons that normally suppress the anti-nociceptor neurons
- **Enkephalin:** It is used by interneurons in lamina II responsible for inhibiting the lamina – I nociceptor-specific spinothalamic neurons
- **Dynorphin:** In hypothalamus, PAG, reticular formation, and dorsal horn.
- **Endogenous morphin:** In terminals forming synapses with neuron having μ -opioid receptors in pain modulating pathways.

Opioid Antagonist: Naloxone

- Used to reverse opioid overdose
- Displaces receptor-bound opioids
- Good for overcoming respiratory and CV depression



Stress induced analgesia

- Is the minimal level of pain perceived when a person is exposed to extreme physical trauma.
- In this situation, person forgets about its injuries and just run for saving his life
- It's a well known phenomenon seen when the soldier is wounded in battle field but feels no pain until the battle is over. The cause is not known may be it is similar to Gate control hypothesis.



Terms frequently used

- **Hyperalgesia**
Excessive pain (e.g due to sun burn)
- **Allodynia**
Pain caused by any other sensation e.g. touch will cause pain.
- **Muscular Pain**
Less blood flow in the muscles (ischemia).
- **Causalgia**
Burning pain.
- **Phantom pain**
Pain felt in an amputated part long after amputation was done.

Thalamic Syndrome

- Obstruction of the thalamogeniculate branch of the posterior cerebral artery
- Affects posterior thalamic nuclei.
- Prolonged severe pain.

Trigeminal neuralgia

- It is excruciating intermittent pain by stimulation of trigger area in the face e.g. Washing of face, combing hair, blast of air on face.
- It results from compression of trigeminal nerve root by blood vessels.

Chronic Pain

- Chronic pain can be considered as bad pain because it persists long after injury and is often refractory to pain killers.
- Chronic pain caused by nerve injury is called neuropathic pain.

Neuropathic pain

- Caused by the damage to peripheral nerve.
- The distal cut end develops a scar tissue forming rounded ball (neuroma) which is sensitive to pressure.
- Repeated activation causes continuous pain.
- Examples post herpetic neuralgia and diabetic neuropathy.

Sites & mechanism of pain relief

- Block production of inflammatory mediators.e.g. Aspirin & nonsteroidal antiinflammatories.
- Sympathectomy can be useful.
- Exogenously administration of opoid like drugs.
- Electrical stimulation of the dorsal column can alleviate pain originating below site of stimulation.
- Selective activation of large diameter afferent fibers by transcutaneous electrical nerve stimulation.
- Stimulation of brainstem sites or administration of drugs which can modify serotonergic or adrenergic neurons e.g. antidepressants.

